American Association of Tissue Banks

The leader in support of quality, safety and availability of cells and tissue

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Suitability Determination for Donors of Human Cellular and Tissue-Based Products, Docket No. 97N-484S

Dear Sir/Madam:

The American Association of Tissue Banks (AATB) welcomes the opportunity to provide comments on the proposed rule of the Food and Drug Administration (FDA) expanding the obligations of tissue banks and manufacturers of human cellular and tissue-based products to screen and test donors for risk factors for and clinical evidence of relevant communicable disease agents and diseases, which FDA published in the *Federal Register* on September 30, 1999.[1]

I. Background

AATB was formed in 1976 to help ensure that transplantable human tissues are safe, of uniform high quality, and supplied in quantities sufficient to meet national needs. The Association's membership currently includes 1,200 individual professionals and 62 AATB-accredited tissue banks engaged in the recovery, processing, storage, and distribution of human tissue. Most of the major tissue banks in the U.S. have gained AATB accreditation. AATB members provide an estimated 90 percent of all tissues intended for clinical use in the United States.

[1] 64 Fed. Reg. 52,696 (1999).

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AATB has long supported balanced government efforts to assure the safety of all human tissues provided for transplantation in the United States. AATB supported, in concept, FDA's promulgation in 1993 of the Interim Rule for human tissue intended for transplantation,[2] whose content closely tracked AATB's own standards. In addition, AATB has supported the principle of mandatory registration for all entities engaged in procuring, processing, or distributing human tissue in the United States.[3] AATB also endorses the idea of basic labeling requirements for human tissues.

The goals of FDA's tissue program are laudatory and consistent with the policies underlying AATB's own requirements for tissue establishments, but the means FDA has chosen to implement the tissue program on occasion not only have troubled AATB and its members, but also, ultimately, have created difficulties for the agency (e.g., heart valves and bone dowels). On these occasions, AATB has registered its objections with FDA.

AATB strongly supports mandatory donor screening and testing to prevent the transmission of communicable diseases from infected donors. In fact, AATB accreditation standards have included such requirements for years. However, AATB and its members again have serious reservations about the means FDA has chosen to implement these requirements. See Part II.A. For example, AATB believes it is inappropriate to require tissue establishments to use only FDA-licensed, –cleared, or –approved tests for prospective donors because, as FDA has recognized, such tests simply do not exist for cadaveric blood.

AATB is also troubled by FDA's further elaboration in the preamble to the proposed rule of the "minimal manipulation" and "homologous use" criteria. AATB continues to have questions and significant reservations about the "minimal manipulation" and "homologous use" criteria FDA is using or will use to determine whether particular tissue-based products will be treated as conventional tissues or as medical devices or biological drugs subject to regulation under the Federal Food, Drug, and Cosmetic Act. Because the preamble accompanying the proposed donor suitability rule revisits these criteria, AATB is again setting forth its views on their appropriateness in these comments. See Part II.B.1.[4]

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[2] 58 Fed. Reg. 65,514 (1993).

[3] 63 Fed. Reg. 26,744 (1998).

[4] AATB explained its position on these criteria in comments submitted to FDA on the Proposed Approach document in 1997 and again in comments submitted on

AATB believes the criteria FDA will use to make jurisdictional determinations cannot be judged separately from the process by which the agency will apply the criteria. AATB is, therefore, also submitting comments on the procedures the agency's Tissue Reference Group appears to be using to make jurisdictional determinations. See Part II.B.2.[5] These procedures are especially important. FDA, through the Tissue Reference Group, has purported to reach significant regulatory decisions about tissue-based products without affording the tissue community prior notice or an opportunity to express views or supply information.

II. Comments on The Proposed Donor Suitability Determination Rule

A. Comments on Specific Provisions

1. Definition of "Donor Medical History Interview" (Proposed Section 1271.3(o))

The proposed definition of "donor medical history interview" does not specifically state that interviews with sources of information about a prospective donor must be in person. The agency should accept not only in-person, face-to-face dialogues, but also written exchanges, telephonic communications, and other forms of communication. AATB assumes that the definition includes communications with friends and life partners who are often valuable sources of information about prospective donors.

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the proposed tissue establishment and registration rule in 1998. AATB has also voiced its reservations about the criteria in other, less formal, communications with FDA.

[5] In a letter dated July 23, 1999, to FDA's Chief Counsel, AATB (through counsel) expressed its intention to submit specific suggestions to improve the existing procedure for determining whether a particular tissue-based article or class of articles should be regulated under the device or drug provisions of the FD&C Act. See Tab A. Determinations by the TRG are already formally subject to FDA's general dispute resolution regulations (21 C.F.R. § 10.75). Nevertheless, AATB is proposing specific reforms of the TRG process, rather than relying on the review process set out in the regulations.

2. Procedure for Identifying Additional "Relevant Communicable Disease Agents or Disease Means" (Proposed Section 1271.3(y))

FDA should specify, in the final rule itself, the procedures it will use to identify additional "relevant communicable disease agents and diseases."[6] Whatever procedure FDA develops should recognize that, except in cases of real urgency, the agency must afford interested parties prior notice and an opportunity to comment before adding a new disease agent or disease to the list under Section 1271.3(y). See 5 U.S.C. § 553(b)(3)(B) (in rulemaking, prior notice is not required when the agency for good cause finds, and incorporates the finding and a brief statement of the reasons therefore in the rules issued, that prior notice is contrary to the public interest).

The notice and comment rulemaking process not only is required by law but also serves several valuable purposes. The tissue community, which historically has responded promptly and effectively to the emergence of a new and potentially significant disease, will in many cases be able to provide FDA with information relevant to the determination whether a new disease or disease agent should be added to the list. In addition, in some cases AATB comments will reveal scientific complexities that otherwise might be unknown to FDA. In addition, with these procedural safeguards, FDA could avoid imposing an additional testing obligation on tissue establishments where there is no test available for a disease. Through comments, tissue establishments also could help FDA avert the unnecessary destruction of tissues already in inventory based on an abrupt decision to add a new disease or disease agent to the list if inventoried tissues are for some scientific reason not amenable to testing.

3. Requirement That "Suitability" Determination Be Based on Both Screening and Testing (Proposed Section 1271.50)

AATB supports proposed Section 1271.50, which provides that a donor is deemed "suitable" based on non-reactive or negative results of both screening and testing. Requiring both screening and testing for all prospective donors will assure that a prospective donor who is deemed unsuitable based on an initial screening, and who is covered by proposed Section 1271.65, will nevertheless be subject to mandatory testing.

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[6] 64 Fed. Reg. at 52,701.

4. Requirement That Donor Specimen Be Collected At the Time of Recovery or Within 48 Hours (Proposed Section 1271.80(b))

AATB is concerned that proposed section 1271.80(b) imposes unduly restrictive time requirements on tissue recovery operations. For cadaveric donors (who are the overwhelming majority of donors), the proposed regulation would require tissue banks to collect blood specimens for testing "at the time of recovery . . . or within 48 hours after recovery." Though it is often desirable to obtain a blood sample for testing as close to the time of death as possible, there can be valid scientific reasons for drawing a specimen pre-mortem. The red blood cell component of post-mortem samples is often affected by hemolysis and hemodilution, both of which can be aggravated by some types of medical intervention. Hemolysis and hemodilution can lead to false positive results and the unnecessary disqualification of tissue from cadaveric donors.

FDA should permit pre-mortem testing for cadaveric donors. Because such donors generally are hospitalized before death, they are subject to frequent monitoring and comprehensive documentation. In addition, such donors are in a controlled environment immediately before death and exposure to disease and disease agents is limited. FDA already is proposing to permit testing up to seven days prior to recovery for living donors, whose exposure to disease immediately before donation will generally be greater because they are not hospitalized.

5. Requirement That Testing Be Performed Using Only FDA Licensed, Cleared, or Approved Products in Accordance with Approved Labeling By CLIA-Certified Laboratories (Proposed Section 1271.80(c))

Proposed section 1271.80(c) should describe the circumstances in which tissue establishments are permitted to use tests that are not FDA-licensed, –cleared, or –approved. As FDA has recognized, there currently are no FDA licensed screening kits for cadaveric blood samples.[7] In addition, there are diseases and disease agents for which an FDA-licensed, –approved, or –cleared test does not exist. There are also diseases and disease agents for which there is a test that has been licensed, approved, or cleared by FDA, but for use only in blood, rather than tissue. In such cases, manufacturers should be permitted to use other appropriate screening measures.[8]

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[7] 62 Fed. Reg. 40,429, 40,434 (1997) (discussing unavailability of FDA licensed screening kits for cadaveric blood specimens).

[8] 64 Fed. Reg. at 52,701.

This section should be amended to permit testing by laboratories that are not certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) but are exempt from CLIA because they are in States (e.g., New York) whose clinical laboratory requirements have been found by the Department of Health and Human Services to be equivalent to or more stringent than CLIA requirements.[9] This section should be further amended to permit testing by foreign laboratories that are subject to requirements that are equivalent to or more stringent than analogous requirements under CLIA.

6. Scope of Regulation of Tissue Screening and Testing Laboratories

FDA should clarify that clinical laboratories are not "establishments" subject to registration and listing with FDA simply because they perform communicable disease testing under contract with tissue banks. FDA states in the preamble to the proposed donor suitability rule that "communicable disease testing and screening [are] . . . steps in the manufacturing process" and notes that the proposed registration and listing rule defines "manufacture" to include "screening" and "testing." 63 Fed. Reg. at 26,754 (proposed Section 1271.3(f)). Facilities whose only role in tissue processing is testing are already excluded from the proposed registration and listing requirements because the proposed definition of "establishment" expressly excludes "an individual . . . under contract to a registered establishment." Id. (proposed Section 1271.3(b)). In addition, because the proposed donor suitability rule provides that all testing must be performed in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), requiring registration for these laboratories is unnecessary.[10] In contrast, facilities engaged in "screening" of prospective tissue donors should be deemed "establishments" under the proposed establishment registration and listing rule because these facilities are not necessarily governed by CLIA.

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[9] See 42 U.S.C. § 263a(p)(2).

[10] Similarly, FDA should clarify that the proposed registration and listing requirements, which are appropriate for conventional tissue establishments, do not apply to physician offices and hospitals who store a limited supply of skin and other tissues so long as these facilities do not engage in other activity encompassed within the definition of "manufacture" in the proposed establishment registration and listing rule. We assume that hospitals retaining autologous tissue, not used in a scheduled surgical procedure, to be used in a subsequent application on the same patient, are exempt from registration and listing because the two applications are essentially a single continuous procedure. See Proposed Section 1271.20(d).

B. FDA's Criteria and Procedure for Jurisdictional Determinations

1. "Minimal Manipulation" and "Homologous Use"

As discussed at length in our comments on the "Proposed Approach" document, the interim rule, and the proposed establishment registration and listing rule (Tabs B-D), AATB believes that FDA's definitions of "minimal manipulation" and "homologous use" offer imperfect and uncertain guidance for determining which tissues should be regulated as devices or drugs. Rather than proposing regulations defining these vague concepts to afford the tissue community some certainty about how their products will be treated, FDA has offered further musings about the meaning of these uncodified criteria. AATB requests that FDA schedule a public meeting to discuss the appropriateness, legality, and practicability of using these criteria to reach jurisdictional determinations.

2. The Tissue Reference Group (TRG)

In early June 1999, AATB received a letter from Dr. Celia Witten of CDRH (Tab E) advising that the Orthopedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee would be meeting on July 27, 1999, to "focus on the classification of bone dowel devices of human origin" and inviting AATB and its members to participate in the panel meeting by presenting testimony and/or submitting written comments. This language suggested that CDRH had already determined that bone dowels should be regulated as medical devices under the FD&C Act.

We now understand that the preliminary determination to treat bone dowels as medical devices was based on a TRG meeting in the fall of 1998 and correspondence between FDA and one manufacturer of bone dowels. Though FDA subsequently amended the agenda of the classification panel meeting to eliminate consideration of the bone dowel issue, the closed procedure used by the agency to determine that bone dowels should be treated as medical devices remains of great concern to AATB and its members.

The TRG apparently holds the view that it has authority to respond to requests for designation from individual product sponsors by issuing either a determination for a particular product or a "recommendation" for an entire class of products. According to the TRG's Annual Report for fiscal year 1998, the TRG has authority to make recommendations for a specific product or for a class of products. Even when the TRG takes action that purports to apply only to a specific manufacturer's product, the action is likely to serve as a precedent for all products in the same class and thus amounts to class-wide regulation.

In issuing class-wide recommendations, the TRG purports to "communicate this information through guidance and revisions of regulations, where appropriate." Nothing in current FDA regulations or in the TRG's standard operating procedures appears to require the TRG to afford affected parties the opportunity to participate in its proceedings, which might result in a "recommendation" for regulation affecting an entire class of tissue-based products.

FDA regulations do not permit the Office of the Ombudsman to issue class-wide jurisdictional determinations based on a request for designation from a single manufacturer. Under 21 C.F.R. Part 3, a sponsor of a premarket approval application or investigational filing for a product is permitted to submit a request for designation (RFD) to the Office of the Ombudsman where the "agency component with primary jurisdiction [of the product] is unclear or in dispute." 21 C.F.R. § 3.7. Within 60 days of the filing date, the Ombudsman is required to "issue a letter of designation to the sponsor . . . specifying the agency component designated to have primary jurisdiction for the premarket review and regulation of the product at issue, and any consulting agency components." Id. § 3.8(b) (emphasis added). This regulation does not authorize the Ombudsman to respond to an RFD with a letter of designation covering all products in the class.[11]

FDA should clarify the TRG's authority. At minimum, the agency should amend the standard operating procedures followed by the TRG to preclude the Group from issuing class-wide "recommendations" based on an assessment of a single product. AATB also urges FDA to: (1) issue a public announcement whenever the TRG determines that a specific tissue-based product is to be regulated under the FD&C Act; and (2) provide general notice whenever the TRG concludes that an RFD might become the basis for treating an entire class of tissue-based products as medical devices or biological drugs under the FD&C Act.

With respect to TRG proceedings generally, FDA should institute the following general procedures for any action taken or proposed by the TRG which could have broad effects on the tissue industry.

First, TRG meetings should be announced in the *Federal Register* or in some other formal fashion, together with a general description of the issues to be discussed. To AATB's knowledge, nothing in the TRG's standard operating procedures assures that all potentially affected manufacturers will be given notice that the TRG intends to consider the jurisdictional status of a particular product.

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[11] At FDA's 1997 public meeting on tissue regulation, the head of FDA's Office of the Ombudsman stated that the TRG process is "a subset" of the Part 3 process.

Second, most TRG meetings should be open to the public. Portions of FDA meetings that are governed by the confidentiality requirements in federal law and FDA regulations should be closed to the public. The TRG has taken the position that its meetings are not required to be open at all because proprietary information is submitted by the sponsor requesting the ruling.[12] In fact, FDA routinely holds open meetings on subjects involving proprietary information, closing only those portions of the meeting that require the disclosure of confidential data. FDA should identify other legitimate legal grounds on which the agency might be required to conceal portions of TRG proceedings from public view.

Third, the TRG's standard operating procedures should direct the Executive Secretary of the Group to publish the group's findings and the basis for its decisions, subject to the confidentiality requirements in federal law and FDA regulations, and that the TRG's standard operating procedures should require the Group to explain jurisdictional determinations on the basis of published criteria.

III. Conclusion

AATB endorses the concept that prospective tissue donors should be screened and tested for communicable diseases. Recognizing the public health significance of preventing disease transmission through tissue donation, AATB's own accreditation procedures already contain donor screening and testing requirements.

AATB reiterates its previously expressed, continuing concerns about the criteria and procedures FDA has been using to make jurisdictional determinations. AATB worries that rigid application of these definitions could lead to the imposition of inappropriate and burdensome labeling, processing, data submission, or other requirements for conventional tissues that have been used successfully by clinicians for many years.

AATB and its members remain troubled by FDA's continuing practice of reaching significant regulatory decisions affecting the entire tissue community without following appropriate procedures. AATB urges FDA to convene a public meeting in which the tissue community and other interested parties can express their concerns about the "minimal manipulation" and "homologous use" criteria. In addition, FDA should reassess the procedures used by the TRG to formulate recommendations for regulation in order to minimize the risk that a recommendation will lead to class-wide regulation without prior notice to or comment by affected parties.

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[12] See TRG Annual Report FY 98.

Sincerely,

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